

WEST**End of Result Set**☐ **Generate Collection** **Print**

L24: Entry 1 of 1

File: JPAB

Mar 8, 1994

PUB-NO: JP406065090A

DOCUMENT-IDENTIFIER: JP 06065090 A

TITLE: PHARMACEUTICAL FOR NASAL ADMINISTRATION

PUBN-DATE: March 8, 1994

INVENTOR-INFORMATION:

NAME

COUNTRY

KATOU, YASUKI

IWATA, KENJI

KAWAGUCHI, YUJI

HAYAKAWA, EIJI

ASSIGNEE-INFORMATION:

NAME

COUNTRY

KYOWA HAKKO KOGYO CO LTD

APPL-NO: JP04221493

APPL-DATE: August 20, 1992

INT-CL (IPC): A61K 37/02; A61K 37/02; A61K 37/02; A61K 47/36

ABSTRACT:

PURPOSE: To provide a pharmaceutical capable of easily and efficiently absorbing G-CSF into the body through its nasal administration, thus hopeful of effects such as curing leucopenia, esp. neutropenia.

CONSTITUTION: The objective pharmaceutical can be obtained by incorporating 0.5-10.0mg/ml of dextran as absorption promoter in a solution of glanulocyte colony stimulating factor (G-CSF).

COPYRIGHT: (C)1994,JPO&Japio

09/720970

WEST Search History

DATE: Tuesday, February 12, 2002

Set Name Query

side by side

Hit Count Set Name

result set

DB=JPAB; PLUR=YES; OP=OR

L24 06065090

1 L24

DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=OR

L23 122 and 11

15 L23

L22 (granulocyte adj1 colony adj1 stimulat\$)

1666 L22

L21 118 and (insulin or polypeptides or vaccines) and powder

55 L21

L20 118 and (insulin or polypeptides or vaccines)

56 L20

L19 L18118 and poder

0 L19

L18 eudragit and 11

75 L18

L17 116 and cellulose

128 L17

L16 115 and (insulin or polypeptides or vaccines)

202 L16

L15 113 and (nasal or mucos\$)

248 L15

L14 113 and 11

0 L14

L13 111 or 112

789 L13

L12 poly adj2 arginine

186 L12

L11 polyarginine

647 L11

L10 19 and (poly adj1 argininE)

0 L10

L9 18 and powder

99 L9

L8 16 and (insulin or polypeptides or vaccines)

111 L8

L7 16 and (insulin or drugs or polypeptides or vaccines)

128 L7

L6 13 and (cellulose)

135 L6

L5 13 and (hydroxypropmethyl adj1 cellulose)

0 L5

L4 11 and (cellulose)

455 L4

L3 L1 and (arginine)

193 L3

L2 L1 and (polyarginine)

0 L2

L1 (mucos\$ or nasal\$) adj2 (preparation or composition)

1063 L1

END OF SEARCH HISTORY

Set Name Query

side by side

Hit Count Set Name

result set

DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=OR

<u>L14</u>	113 and (eudragit or chitosan)	4	<u>L14</u>
<u>L13</u>	L12 and cellulose	30	<u>L13</u>
<u>L12</u>	mucosal adj2 (preparation or composition)	105	<u>L12</u>
<u>L11</u>	110 and (hydroxypropylmethyl adj1 cellulose)	18	<u>L11</u>
<u>L10</u>	17 and (proteins or insulin or drugs)	130	<u>L10</u>
<u>L9</u>	18 and ((cationic adj1 polymer\$) or eudragit or chitosan)	11	<u>L9</u>
<u>L8</u>	17 and (hydroxypropylmethyl adj1 cellulose)	18	<u>L8</u>
<u>L7</u>	16 and insulin	130	<u>L7</u>
<u>L6</u>	\$nasal adj1 (preparation or compositionN)	550	<u>L6</u>

DB=EPAB,DWPI; PLUR=YES; OP=OR

<u>L5</u>	193372.pn. and chitosan	0	<u>L5</u>
-----------	-------------------------	---	-----------

DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=OR

<u>L4</u>	L3 and (protein or insulin)	14	<u>L4</u>
<u>L3</u>	L2 and powder	23	<u>L3</u>
<u>L2</u>	((edragit or chitos\$) same (hydroxypropylmethyl adj1 cellulose)) and (drug\$ or protein\$ or insulin or pharmaceuticals)	45	<u>L2</u>
<u>L1</u>	(edragit or chitos\$) same (insulin or (growth adj1 factor\$) or antigens) same (hydroxypropylmethyl adj1 cellulose)	1	<u>L1</u>

END OF SEARCH HISTORY

WEST

☐

L12: Entry 19 of 101

File: USPT

Oct 26, 1999

DOCUMENT-IDENTIFIER: US 5972373 A

TITLE: Taste masking pharmaceutical composition for oral administration

Brief Summary Text (5):

For example, Japanese Patent Kokai 49-81526 discloses a method which comprises dissolving a macrolide antibiotic in an inert volatile organic solvent wherein a wall polymer selected from the group consisting of polyvinylacetal diethylaminoacetate (hereinafter referred to as "AEA"), cellulose acetate dibutylaminohydroxypropyl ether, aminoalkylmethacrylate copolymer E (trade name; Eudragit E) and ethyl cellulose and at least one selected from the group consisting of a wax, a higher fatty acid and a salt insoluble in the higher fatty acid are dissolved or dispersed; spray-drying the solution; and collecting the resulting encapsulated particles of the macrolide antibiotic.

Brief Summary Text (7):

As an example of a pharmaceutical mixture for masking a taste of an unpleasantly tasting basic drug, EP Patent No. 69097 discloses that a dry powder for a pharmaceutical mixture comprising an encapsulated bad tasting drug in a form insoluble at high pH.

Brief Summary Text (21):

The composition for oral administration of the present invention can be formulated in the unit dose forms such as granules, powders, capsules, tablets, dry syrups, preferably dry syrups.

Detailed Description Text (4):

600 g of glyceryl monostearate was melted at about 100.degree. C., and 100 g of Eudragit E was dispersed and dissolved therein. In the mixture was further dispersed 300 g of erythromycin, followed by spray-cooling granulation using a spray-dryer at an inlet temperature of 80.degree. C. at a rotary disk rotation rate of 20000 rpm. Then, the resulting granules were tumbled and shaken by a VG coater (Kikusui Manufacturing Ltd.) at a jacket temperature of 40.degree. C. at a rotation rate of 15 rpm for 2 hours to give about 950 g of a powder wherein the glyceryl monostearate was in the .beta.-crystal form.

Detailed Description Text (6):

600 g of glyceryl monostearate was melted at about 100.degree. C., and 100 g of Eudragit E was dispersed and dissolved therein. In the mixture was further dispersed 300 g of clarithromycin, followed by spray-cooling granulation using a spray-dryer at an inlet temperature of 80.degree. C. at a rotary disk rotation rate of 20000 rpm. Then, the resulting granules were tumbled and shaken by a VG coater (Kikusui Manufacturing Ltd.) at a jacket temperature of 40.degree. C. at a rotation rate of 15 rpm for 2 hours to give about 950 g of a powder wherein the glyceryl monostearate was in the .beta.-crystal form.

Detailed Description Text (8):

To 333 g of the powder of Example 1 were added 300 g of sorbitol, 20 g of magnesium oxide and 347 g of starch, followed by homogeneous mixing. The mixture was subjected to fluidized bed granulation with water to give granules.

Detailed Description Text (10):

To 333 g of the powder of Example 1 were added 500 g of mannitol, 15 g of magnesium oxide and 152 g of starch, followed by homogeneous mixing. The resulting mixture was

subjected to fluidized bed granulation with water to give granules.

Detailed Description Text (12):

To 333 g of the powder of Example 1 were added 450 g of xylitol, 10 g of magnesium oxide and 162 g of starch, followed by homogeneous mixing. The resulting mixture was subjected to fluidized bed granulation with water to give granules.

Detailed Description Text (14):

To 333 g of the powder of Example 2 were added 300 g of sorbitol, 300 g of mannitol, 5 g of magnesium oxide, 10 g of sodium carboxymethyl cellulose and 52 g of crystalline cellulose, followed by homogeneous mixing. The resulting mixture was subjected to fluidized bed granulation with water to give granules.

Detailed Description Text (16):

To 333 g of the powder of Example 1 were added 300 g of sorbitol, 300 g of mannitol, 10 g of sodium carboxymethyl cellulose and 47 g of starch, followed by homogeneous mixing. The resulting mixture was subjected to fluidized bed granulation using the separately-prepared suspension of 10 g of magnesium oxide in water as a binding solvent to give granules.

Detailed Description Text (18):

To 333 g of the powder of Example 2 were added 300 g of sorbitol, 10 g of sodium carboxymethyl cellulose and 347 g of starch, followed by homogeneous mixing. The resulting mixture was subjected to fluidized bed granulation using the separately-prepared suspension of 10 g of magnesium oxide in water as a binding solvent to give granules.

Detailed Description Text (20):

To 333 g of the powder of Example 2 were added 400 g of sorbitol, 229 g of xylitol, 10 g of sodium carboxymethyl cellulose, 5 g of magnesium oxide, 20 g of hydroxylpropyl cellulose and 3 g of saccharin sodium, followed by homogeneous mixing. The mixture was subjected to fluidized bed granulation using water as a granulating solvent to give granules, 1 g of which was then suspended in about 5 ml of water, whereby a syrup was obtained.

Detailed Description Text (22):

To 333 g of the powder of Example 2 were added 300 g of sorbitol, 100 g of mannitol, 100 g of xylitol, 100 g of maltitol, 10 g of sodium carboxymethyl cellulose, 20 g of magnesium oxide, 14 g of starch, 20 g of hydroxylpropyl cellulose and 3 g of saccharin sodium, followed by homogeneous mixing. The resulting mixture was subjected to fluidized bed granulation using water as a granulating solvent to give a dry-syrup containing 10% clarithromycin.

Detailed Description Text (24):

To 333 g of the powder of Example 1 were added 500 g of mannitol, 20 g of magnesium oxide, 125 g of starch, 20 g of hydroxylpropyl cellulose and 2 g of sodium carboxymethyl cellulose, followed by homogeneous mixing. The resulting mixture was subjected to fluidized bed granulation with water to give granules.

Detailed Description Text (26):

600 g of glyceryl monostearate was melted at about 100.degree. C., and 100 g of Eudragit E was dispersed and dissolved therein. In the mixture was further dispersed 300 g of erythromycin, followed by spray-cooling granulation using a spray-dryer at an inlet temperature of 80.degree. C. at a rotary disk rotation rate of 20000 rpm. Then, the resulting granules were tumbled and shaken by a VG coater (Kikusui Manufacturing Ltd.) at a jacket temperature of 45.degree. C. at a rotation rate of 15 rpm for an hour to give about 950 g of a powder wherein the glyceryl monostearate was in the .beta.-crystal form. To 333 g of the resulting powder were added 300 g of sorbitol, 300 g of mannitol, 10 g of sodium carboxymethyl cellulose and 47 g of starch, followed by homogeneous mixing. The resulting mixture was subjected to fluidized bed granulation using the separately-prepared suspension of 10 g of magnesium oxide in water as a binding solvent to give granules.

Detailed Description Text (28):

600 g of glyceryl monogstearate was melted at about 100.degree. C., and 100 g of

Eudragit E was dispersed and dissolved therein. In the mixture was further dispersed 300 g of erythromycin, followed by spray-cooling granulation using a spray-dryer at an inlet temperature of 70.degree. C. at a rotary disk rotation rate of 15000 rpm. Then, the granules were tumbled and shaken by a VG coater (Kikusui Manufacturing Ltd.) at a jacket temperature of 35.degree. C. at a rotation rate of 15 rpm for 3 hours to give about 950 g of a powder wherein the glyceryl monostearate was in the .beta.-crystal form. To 333 g of the resulting powder were added 300 g of mannitol, 10 g of sodium carboxymethyl cellulose and 347 g of starch, followed by homogeneous mixing. The resulting mixture was subjected to fluidized bed granulation using the separately-prepared suspension of 10 g of magnesium oxide in water as a binding solvent to give granules.

Detailed Description Text (30):

600 g of glyceryl monostearate was melted at about 100.degree. C., and 100 g of Eudragit E was dispersed and dissolved therein. In the mixture was further dispersed 300 g of erythromycin, followed by spray-cooling granulation using a spray-dryer at an inlet temperature of 80.degree. C. at a rotary disk rotation rate of 20000 rpm to give about 950 g of a powder wherein the glyceryl monostearate was in the .alpha.-crystal form.

Detailed Description Text (32):

To 333 g of the powder of Control Example 1 were added 300 g of sorbitol, 20 g of magnesium oxide and 347 g of starch, followed by homogeneous mixing. The mixture was subjected to fluidized bed granulation with water to give granules.

CLAIMS:

1. A pharmaceutical composition for oral administration for masking a bitter taste comprising an unpleasantly tasting drug, a polymer selected from the group consisting of polyvinylacetal diethylaminoacetate, aminoalkylmethacrylate copolymer E or a mixture thereof, and a monoglyceride in the .beta.-crystal form, said composition is produced by the method which comprises the steps of:

dispersing or dissolving said polymer in a monoglyceride which is heated to a temperature equal to or higher than the melting point;

granulating an unpleasantly tasting drug using the resulting mixture of polymer and monoglyceride;

cooling the granules; and

and causing the .alpha.-crystal form of monoglyceride in the granules to convert into the .beta.-crystal thereof.

3. The composition for oral administration according to claim 1 wherein the high polymer is polyvinylacetal diethylaminoacetate,

aminoalkylmethacrylate copolymer E or a mixture thereof,

and the monoglyceride is glyceryl monostearate.

5. A method for masking a taste of an unpleasant tasting drug, comprising using a high polymer selected from the group consisting of polyvinylacetal diethylaminoacetate, aminoalkylmethacrylate copolymer E or a mixture thereof, and a monoglyceride in the .beta.-crystal form, wherein said method comprises the steps of:

dispersing or dissolving said polymer in a monoglyceride which is heated to a temperature equal to or higher than the melting point;

granulating an unpleasantly tasting drug using the resulting mixture of polymer and monoglyceride;

cooling the granules; and

causing the .alpha.-crystal form of monoglyceride in the granules to convert into the .beta.-crystal thereof.

WEST



Generate Collection

Print

L2: Entry 37 of 45

File: DWPI

Jan 5, 1995

DERWENT-ACC-NO: 1995-051726

DERWENT-WEEK: 199507

COPYRIGHT 2002 DERWENT INFORMATION LTD

TITLE: Topical aq. compsn. for treating glaucoma - contains bispilocarpic acid diesters, viscosity enhancing agent and buffer

Basic Abstract Text:

The pref. viscosity enhancing agent is sodium carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone, polyvinylalcohols, dextrans, polyacrylic acids, chitosans, hyaluronic acid or esp. hydroxypropylmethyl cellulose (HPMC). The buffer is pref. a phosphate, borate, acetate, or citrate buffer esp. citrate buffer at 50-100 mM. The bispilocarpic acid diester is pref. O,O'-diacyl (1,4-xylylene) bispilocarpate esp. O,O'-dicyclopropylcarbonyl (1,4-xylylene) or (1,6-hexylene) bispilocarpate.

Basic Abstract Text:

ADVANTAGE - The compsn. increases the total drug delivery to the eye and prolongs the duration of action whilst simultaneously reducing the peak level and associated side effects.

Basic Abstract Text (2):

The pref. viscosity enhancing agent is sodium carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone, polyvinylalcohols, dextrans, polyacrylic acids, chitosans, hyaluronic acid or esp. hydroxypropylmethyl cellulose (HPMC). The buffer is pref. a phosphate, borate, acetate, or citrate buffer esp. citrate buffer at 50-100 mM. The bispilocarpic acid diester is pref. O,O'-diacyl (1,4-xylylene) bispilocarpate esp. O,O'-dicyclopropylcarbonyl (1,4-xylylene) or (1,6-hexylene) bispilocarpate.

Basic Abstract Text (4):

ADVANTAGE - The compsn. increases the total drug delivery to the eye and prolongs the duration of action whilst simultaneously reducing the peak level and associated side effects.

WEST



Generate Collection

Print

L20: Entry 12 of 101

File: PGPB

Mar 14, 2002

DOCUMENT-IDENTIFIER: US 20020032429 A1

TITLE: Delivery device and method for its operation

Detail Description Paragraph (7):

[0025] The invention may assist in solving special problems in connection with sensitive compounds susceptible to degradation or denaturation under mechanical stress, such as high shear forces. Compounds of high molecular weight may be of this type, high molecular weight hormones for example growth hormones or prostaglandins. The invention may also assist in solving special problems in connection with medical materials requiring a preparation step immediately prior to the infusion, typically a mixing of two or more components, which all may be fluid or may include a solid as when dissolving a lyophilized powder in a solvent, such as hormones or prostaglandins.

WEST

End of Result Set

☐

L8: Entry 14 of 14

File: DWPI

Jan 18, 1990

DERWENT-ACC-NO: 1990-062778

DERWENT-WEEK: 199009

COPYRIGHT 2003 DERWENT INFORMATION LTD

TITLE: New solid prepn. of probucol - comprises micro-powder compsn. of probucol with one or more gastro-enteric soluble macromolecular cpds. e.g. methacrylic acid copolymer L

PATENT-ASSIGNEE:

ASSIGNEE

TAKADA SEIYAKU KK

CODE

TAKAN

PRIORITY-DATA: 1988JP-0162480 (July 1, 1988)

PATENT-FAMILY:

PUB-NO

PUB-DATE

LANGUAGE

PAGES

MAIN-IPC

JP 02015027 A

January 18, 1990

005

APPLICATION-DATA:

PUB-NO

APPL-DATE

APPL-NO

DESCRIPTOR

JP 02015027A

July 1, 1988

1988JP-0162480

INT-CL (IPC): A61K 9/16; A61K 31/10; A61K 47/30

ABSTRACTED-PUB-NO: JP 02015027A

BASIC-ABSTRACT:

New solid prepn. of probucol, comprise a micropowder compsn. obtd. with pulverisation of (1) probucol and (2) one or more of gastro-enteric soluble macromolecular cpds. of aminoalkylmethacrylate copolymer E, methacrylic acid copolymer L, acetic acid phthalic acid cellulose, hydroxy propylmethylcellulose acetate succinate, polyvinylacetal diethylaminoacetate, and hydroxypropylmethyl cellulose phthalate.

USE/ADVANTAGE - Solid prepn. of probucol useful for therapy of high cholesterol diseases.

In an example, (1) probucol (10 wt.pts.), lactose (10), and aminoalkyl methacrylate copolymer E (10) are mixed and pulverised with a mill for 30 min. to form a micropowder compsn. (average grain size: 10 micron or less), to which carboxymethylcellulose (3) and magnesium stearate (1) are added and formed into granules. (2) Granules comprised probucol (10 wt.pts.), lactose (10), methacrylic acid copolymer - L (10), carboxymethylcellulose (3) and magnesium stearate (1). (3) Granules consisting of probucol (10 wt.pts.), lactose (10), acetic phthalic acid cellulose (10), carboxymethylcellulose (3) and magnesium stearate (1).

CHOSEN-DRAWING: Dwg.0/1

TITLE-TERMS: NEW SOLID PREPARATION PROBUCOL COMPRISE MICRO POWDER COMPOSITION
PROBUCOL ONE MORE GASTRO ENTERAL SOLUBLE MACROMOLECULAR COMPOUND METHACRYLIC ACID
COPOLYMER

WEST

Generate Collection

Print

L7: Entry 18 of 21

File: JPAB

Jan 18, 1990

PUB-NO: JP402015027A

DOCUMENT-IDENTIFIER: JP 02015027 A

TITLE: NOVEL PROBUCOL SOLID PREPARATION

PUBN-DATE: January 18, 1990

INVENTOR-INFORMATION:

NAME

COUNTRY

DOI, NORIHIDE

IKUTA, NAOHITO

TOMIZAWA, HIROO

ASSIGNEE-INFORMATION:

NAME

COUNTRY

TAKADA SEIYAKU KK

APPL-NO: JP63162480

APPL-DATE: July 1, 1988

INT-CL (IPC): A61K 31/10; A61K 9/16; A61K 31/10; A61K 47/30; A61K 47/38

ABSTRACT:

PURPOSE: To obtain a solid preparation having enhanced solubility and remarkably improved bioavailability and useful as a serum lipid improving drug by preparing a powder composition obtained by pulverizing a specific gastric or enteric high polymer compound and probucol together.

CONSTITUTION: The aimed solid preparation obtained by pulverizing a gastric high polymer compound selected from an aminoalkylmethacrylate copolymer E and polyvinylacetaldiethylaminoacetate or enteric high polymer compound selected from methacrylic acid copolymer L, acetic acid phthalic acid acetate and hydroxypropylmethylcellulosephthalate and probucol together and preparing the obtained fine powder composition into a solid agent for internal use, e.g., inhalt, subtilized granule, granule or capsule by a conventional preparation method. The high polymer compound is preferably used at an amount of 0.5-10 times in weight based on the probucol.

COPYRIGHT: (C) 1990, JPO&Japio

WEST

Generate Collection

Print

L26: Entry 28 of 32

File: JPAB

May 13, 1992

PUB-NO: JP404139200A
DOCUMENT-IDENTIFIER: JP 04139200 A
TITLE: FIXATION OF PROTEIN

PUBN-DATE: May 13, 1992

INVENTOR-INFORMATION:

NAME

COUNTRY

KEZUKA, HIROAKI

YOSHINO, SAEKO

ISHIBASHI, HITOSHI

SHIMIZU, NORIO

ASSIGNEE-INFORMATION:

NAME

COUNTRY

HITACHI LTD

APPL-NO: JP02260569

APPL-DATE: October 1, 1990

INT-CL (IPC): C07K 17/14; C07K 15/28; C12N 11/00

ABSTRACT:

PURPOSE: To simplify recovery and purification of a protein by binding the protein to a specified hapten and fixing the resultant protein-conjugated hapten to a carrier through an anti-hapten monoclonal antibody.

CONSTITUTION: A protein-conjugated hapten (4-3) is initially obtained by using a hapten (preferably dinitrophenyl) 3 capable of readily binding to a protein 4. The resultant protein-conjugated hapten (4-3) is then fixed to a carrier 1 using an anti-hapten monoclonal antibody 2 so as to be used for the objective recovery.

COPYRIGHT: (C)1992,JPO&Japio

WEST☐ **Generate Collection** **Print**

L19: Entry 88 of 92

File: DWPI

Jan 18, 1990

DERWENT-ACC-NO: 1990-062778

DERWENT-WEEK: 199009

COPYRIGHT 2002 DERWENT INFORMATION LTD

TITLE: New solid prepn. of probucol - comprises micro-powder compsn. of probucol with one or more gastro-enteric soluble macromolecular cpds. e.g. methacrylic acid copolymer L

PATENT-ASSIGNEE:

ASSIGNEE

TAKADA SEIYAKU KK

CODE

TAKAN

PRIORITY-DATA: 1988JP-0162480 (July 1, 1988)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
JP 02015027 A	January 18, 1990		005	

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
JP02015027A	July 1, 1988	1988JP-0162480	

INT-CL (IPC): A61K 9/16; A61K 31/10; A61K 47/30

ABSTRACTED-PUB-NO: JP02015027A

BASIC-ABSTRACT:

New solid prepn. of probucol, comprise a micropowder compsn. obtd. with pulverisation of (1) probucol and (2) one or more of gastro-enteric soluble macromolecular cpds. of aminoalkylmethacrylate copolymer E, methacrylic acid copolymer L, acetic acid phthalic acid cellulose, hydroxy propylmethylcellulose acetate succinate, polyvinylacetal diethylaminoacetate, and hydroxypropylmethyl cellulose phthalate.

USE/ADVANTAGE - Solid prepn. of probucol useful for therapy of high cholesterol diseases.

In an example, (1) probucol (10 wt.pts.), lactose (10), and aminoalkyl methacrylate copolymer E (10) are mixed and pulverised with a mill for 30 min. to form a micropowder compsn. (average grain size: 10 micron or less), to which carboxymethylcellulose (3) and magnesium stearate (1) are added and formed into granules. (2) Granules comprised probucol (10 wt.pts.), lactose (10), methacrylic acid copolymer - L (10), carboxymethylcellulose (3) and magnesium stearate (1). (3) Granules consisting of probucol (10 wt.pts.), lactose (10), acetic phthalic acid cellulose (10), carboxymethylcellulose (3) and magnesium stearate (1).

CHOSEN-DRAWING: Dwg.0/1

TITLE-TERMS: NEW SOLID PREPARATION PROBUCOL COMPRISE MICRO POWDER COMPOSITION
PROBUCOL ONE MORE GASTRO ENTERAL SOLUBLE MACROMOLECULAR COMPOUND METHACRYLIC ACID
COPOLYMER

WEST

Generate Collection

Print

L17: Entry 105 of 128

File: USPT

Oct 28, 1997

DOCUMENT-IDENTIFIER: US 5681814 A
TITLE: Formulated IGF-I Composition

Brief Summary Paragraph Right (4):

Insulin-like growth factor I (IGF-I) is a polypeptide naturally occurring in human body fluids, for example, blood and human cerebral spinal fluid. Most tissues and especially the liver produce IGF-I together with specific IGF-binding proteins. These molecules are under the control of growth hormone (GH). Like GH, IGF-I is a potent anabolic protein. See Tanner et al., Acta Endocrinol., 84: 681-696 (1977); Uthne et al., J. Clin. Endocrinol. Metab., 39: 548-554 (1974)). IGF-I has been isolated from human serum and produced recombinantly. See, e.g., EP 123,228 and 128,733.

Brief Summary Paragraph Right (6):

Human growth hormone (hGH) is a single-chain polypeptide consisting of 191 amino acids (molecular weight 21,500). Disulfide bonds link positions 53 and 165 and positions 182 and 189. Niall, Nature, New Biology, 230: 90 (1971). Human GH is a potent anabolic agent, especially due to retention of nitrogen, phosphorus, potassium, and calcium. Treatment of hypophysectomized rats with GH can restore at least a portion of the growth rate of an intact animal. Moore et al., Endocrinology, 122: 2920-2926 (1988). Among its most striking effects in hypopituitary (GH-deficient) subjects is accelerated linear growth of bone growth plate cartilage resulting in increased stature. Kaplan, Growth Disorders in Children and Adolescents (Springfield, Ill.: Charles C. Thomas, 1964).

Brief Summary Paragraph Right (17):

Various methods for formulating proteins or polypeptides have been described. These include EP 267,015 published May 11, 1988; EP 308,238 published Mar. 22, 1989; and EP 312,208 published Apr. 19, 1989, which disclose formulation of a polypeptide growth factor having mitogenic activity, such as transforming growth factor-.beta. (TGF-.beta.), in a polysaccharide such as methylcellulose; EP 261,599 published Mar. 30, 1988 disclosing human topical applications containing growth factors such as TGF-.beta.; EP 193,917 published Sep. 10, 1986, which discloses a slow-release composition of a carbohydrate polymer such as a cellulose and a protein such as a growth factor; GB Pat. No. 2,160,528 granted Mar. 9, 1988, describing a formulation of a bioactive protein and a polysaccharide; and EP 193,372 published Sep. 3, 1986, disclosing an intranasally applicable powdery pharmaceutical composition containing an active polypeptide, a quaternary ammonium compound, and a lower alkyl ether of cellulose. See also U.S. Pat. No. 4,609,640 issued Sep. 2, 1986 disclosing a therapeutic agent and a water-soluble chelating agent selected from polysaccharides, celluloses, starches, dextroses, polypeptides, and synthetic polymers able to chelate Ca and Mg; and JP 57/026625 published Feb. 12, 1982 disclosing a preparation of a protein and water-soluble polymer such as soluble cellulose.

Brief Summary Paragraph Right (19):

Furthermore, preservatives containing a quaternary ammonium salt have been added to chemical drug formulations to prevent growth of bacteria. See, e.g., Remington's Pharmaceutical Sciences, 18th edition (definition of benzethonium chloride), Martindale, The Extra Pharmacopeia, 28th edition (p.550, entry on benzethonium chloride), United States Pharmacopeia, 22nd edition (pp. 146-147, entries on benzethonium chloride topical solution and tincture), Handbook on Injectable Drugs, 5th edition (p. 246, entry on diphenhydramine HCl, which contains 0.1% benzethonium chloride; pp. 396-397, entry on ketamine HCl, which contains 0.1 mg/ml of benzethonium chloride; and pp. 695-696, entry on Vidarabine, which contains 0.1 mg benzethonium chloride). Another example is the formulation of octreotide in benzalkonium chloride for nasal application as described in GB Appln. 2,193,891 published Feb. 24, 1988. The preservatives have been used in parenteral formulations at low concentrations, and in

antiseptic washes for wound care at higher concentrations. In addition, a mixture of a physiologically active polypeptide with a quaternary ammonium compound and a lower alkyl ether of cellulose is disclosed, wherein the quaternary ammonium compound is added to improve stability and preservability. EP 193,372.

Drawing Description Paragraph Right (27):

As used herein, "IGF-I" refers to insulin-like growth factor from any species, including bovine, ovine, porcine, equine, and preferably human, in native-sequence or in variant form, and from any source, whether natural, synthetic, or recombinant. Preferred herein for animal use is that form of IGF-I from the particular species being treated, such as porcine IGF-I to treat pigs, ovine IGF-I to treat sheep, bovine IGF-I to treat cattle, etc. Preferred herein for human use is human native-sequence, mature IGF-I, more preferably without a N-terminal methionine, prepared, e.g., by the process described in EP 230,869 published Aug. 5, 1987; EP 128,733 published Dec. 19, 1984; or EP 288,451 published Oct. 26, 1988. More preferably, this native-sequence IGF-I is recombinantly produced and is available from Genentech, Inc., South San Francisco, Calif. for clinical investigations. Also preferred for use is IGF-I that has a specific activity greater than about 14,000 units/mg as determined by radioreceptor assay using placenta membranes, such as that available from KabiGen AB, Stockholm, Sweden.

Drawing Description Paragraph Right (29):

As used herein, "GH" refers to growth hormone from any species, including bovine, ovine, porcine, equine, and preferably human, in native-sequence or in variant form, and from any source, whether natural, synthetic, or recombinant. Preferred herein for animal use is that form of GH from the particular species being treated, such as porcine GH to treat pigs, ovine GH to treat sheep, bovine GH to treat cattle, etc. Preferred herein for human use is human native-sequence, mature GH with or without a methionine at its N-terminus. Also preferred is recombinant hGH, i.e., that produced by means of recombinant DNA technology. More preferred is methionyl human growth hormone (met-hGH) produced in *E. coli*, e.g., by the process described in U.S. Pat. No. 4,755,465 issued Jul. 5, 1988 and Goeddel et al., *Nature*, 282: 544 (1979). Met-hGH, which is sold under the trademark PROTROPIN.RTM. by Genentech, Inc., is identical to the natural polypeptide, with the exception of the presence of an N-terminal methionine residue. This added amino acid is a result of the bacterial protein synthesis process.

Drawing Description Paragraph Right (38):

For parenteral administration, in one embodiment, the IGF-I and GH are formulated generally by mixing each at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to polypeptides.

Drawing Description Paragraph Right (40):

The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; glycine; amino acids such as glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, mannose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; nonionic surfactants such as polysorbates, poloxamers, or PEG; and/or neutral salts, e.g., NaCl, KCl, MgCl.sub.2, CaCl.sub.2, etc.

Drawing Description Paragraph Right (61):

The IGF-I formulation of this invention can be used to treat any condition that would benefit from treatment with IGF-I, including, for example, diabetes, chronic and acute renal disorders, such as chronic renal insufficiency, necrosis, etc., obesity, hyperinsulinemia, GH-insufficiency, Turner's syndrome, short stature, undesirable symptoms associated with aging such as increasing lean mass to fat ratios, immuno-deficiencies including increasing CD4 counts and increasing immune tolerance, catabolic states associated with wasting, etc., Laron dwarfism, insulin resistance, and so forth.

Drawing Description Paragraph Right (65):

If the IGF-I is administered together with insulin, the latter is used in lower amounts than if used alone, down to amounts which by themselves have little effect on blood glucose, i.e., in amounts of between about 0.1 IU/kg/24 hour to about 0.5 IU/kg/24 hour.

Detailed Description Paragraph Right (3):

Alzet osmotic pumps (Alza, Palo Alto, Calif.) were implanted to deliver continuously either excipient (10mM citrate buffer and 126 mM NaCl, pH 6.0) or recombinant human IGF-I (produced in E. coli as a Z--Z fusion polypeptide by the process generally described in EP 230,869 published Aug. 5, 1987, or available commercially from KabiGen AB, Stockholm, Sweden (specific activity >14,000 U/mg by radioreceptor assay using placental membranes), or available for clinical investigations from Genentech, Inc., South San Francisco). The IGF-I was dissolved at 5 mg/ml in 10 mM citrate buffer and 126 mM NaCl, pH 6.0 and delivered to the rats at a rate of 120 .mu.g/rat per day (equivalent to 1.2 mg/kg/day assuming that the rats weigh 100 g each). This rate represents a submaximal dose that gives a consistent body weight gain in this model.

Detailed Description Paragraph Right (36):

The results shown herein have significance in medicine and agriculture in any situation where GH or IGF-I treatment is used. This regime of combined IGF-I and GH treatment would allow smaller doses of GH (approximately 25-fold less) to be given to produce equivalent responses to treatment with GH alone. This would be of particular importance in situations where the side effects of GH treatment (i.e., hyperinsulinemia, hyperglycemia) should be minimized. In diabetes, combined GH and IGF-I treatment, with smaller GH doses being possible, would minimize the insulin-resistant effect of the administered GH. In patients where the anabolic effect of GH is reduced, possibly by a reduced ability to produce an IGF-I response to the administered GH, co-treatment with GH and IGF-I would also be expected to give a larger anabolic response.

Detailed Description Paragraph Right (37):

A broad class of patients where the regime of combined GH and IGF-I treatment would be beneficial is in adult patients where the IGF-I response to GH is naturally reduced. In adults, the unwanted effects of GH (insulin resistance) may be a direct consequence of a reduced IGF-I response to administered GH. In adults, the co-administration of GH and IGF-I might be viewed as restoring the situation in a younger animal where there is a more vigorous IGF-I response to GH treatment.

Detailed Description Paragraph Right (45):

The fall in blood glucose caused by an injection of IGF-I is a rapid response that can be easily measured and can serve as a reasonable bioassay for the "insulin-like" activity, or bioactivity in vivo, of IGF-I.

Other Reference Publication (4):

Guler et al., "S.C. Infusion of Recombinant Human Insulin-like Growth Factor I (rhIGF I) Stimulates Growth of Hypophysectomized Rats Continuously During 18 Days", 1st European Congress of Endocrinology, Copenhagen, Jensen & Christiansen, eds., 103:12-390, (Jun. 21-25, 1987).

Other Reference Publication (5):

Guler et al. "Effects of recombinant insulin-Like growth factor I on insulin secretion and renal function in normal human subjects", Proc. Natl. Acad. Sci. USA, 86: 2868-2872 (1989).

Other Reference Publication (6):

Schoenle et al., "Comparison of in vivo effects of insulin-like growth factors I and II and of growth hormone in hypophysectomized rats", Acta Endocrin., 108: 167-174 (1985).

Other Reference Publication (7):

Skottner et al., "Recombinant human insulin-like growth factor: testing the somatomedin hypothesis in hypophysectomized rats", J. Endocr., 112: 123-132 (1987).

Other Reference Publication (8):

Skottner et al., "Growth Responses in a Mutant Dwarf Rat to Human Growth Hormone and Recombinant Human Insulin-Like Growth Factor I", Endocrinology, 124(5): 2519-2526 (1989).

Other Reference Publication (11):

Guler et al., "Short-term metabolic effects of recombinant human insulin-like growth

factor I in healthy adults", N. Engl. J. Med., 317(3): 137-140 (1987).

Other Reference Publication (13):

Guler et al., "Recombinant human insulin-like growth factor I stimulates growth and has distinct effects on organ size in hypophysectomized rats", Proc. Natl. Acad. Sci. USA, 85: 4889-4893 (1988).

Other Reference Publication (15):

Scheiwiller et al., "Growth restoration of insulin-deficient diabetic rats by recombinant human insulin-like growth factor I", Nature, 323: 169-171 (1986).

Other Reference Publication (23):

Vetter et al., "Human Fetal and Adult Chondrocytes: Effects of insulinlike growth factors I and II, insulin and growth hormone on clonal growth", J. Clin. Invest., 7: 1903-1908 (1986).

Other Reference Publication (25):

Isgaard et al., "Pulsatile intravenous growth hormone (GH) infusion to hypophysectomized rats increases insulin-like growth factor I messenger ribonucleic acid in skeletal tissues more effectively than continuous GH infusion", Endocrinology, 123(6): 2605-2610 (1988).

Other Reference Publication (32):

Otonkoski et al., "Effects of growth hormone and insulin-like growth factor I on endocrine function of human fetal islet-like cell clusters during long-term tissue culture", Diabetes, 37: 1678-1683 (1988).

Other Reference Publication (34):

Zezulak and Green, "The Generation of Insulin-Like Growth Factor-1-Sensitive Cells by Growth Hormone Action", Science, 233: 551-553 (1986).

Other Reference Publication (35):

Young et al., "Growth hormone and testosterone can independently stimulate the growth of hypophysectomized prepubertal lambs without any alteration in circulating concentrations of insulin-like growth factors", J. Endocrin., 121: 563-570 (1989).

Other Reference Publication (40):

Ernst and Froesch, "Growth hormone dependent stimulation of osteoblast-like cells in serum-free cultures via local synthesis of insulin-like growth factor I," Biochem. Biophys. Res. Commun., 151(1): 142-147 (1988).

Other Reference Publication (41):

Smith et al., "Growth Hormone Stimulates Insulin-like Growth Factor I Actions on Adult Articular Chondrocytes", J. Orthop. Res., 7: 198-207 (1989).

Other Reference Publication (42):

Merchav et al., "Enhancement of Human Granulopoiesis In Vitro by Biosynthetic Insulin-like Growth Factor I/Somatomedin C and Human Growth Hormone", J. Clin. Invest., 81: 791-797 (1988).

Other Reference Publication (44):

Lindahl et al., "Growth hormone in vivo potentiates the stimulatory effect of insulin-like growth factor-1 on colony in vitro on colony formation of epiphyseal chondrocytes isolated from hypophysectomized rats", Endocrinol., 121(3): 1070-075 (1987).

Other Reference Publication (45):

van Neste et al., "Cellular distribution of somatogenic receptors and insulin-like growth factor-I mRNA in the rat liver", J. Endocr., 199: 69-74 (1988).

Other Reference Publication (46):

Namba et al., "Insulin-Like Growth Factor-I Action on Growth Hormone Secretion and Messenger Ribonucleic Acid Levels: Interaction with Somatostatin", Endocrinol., 124(4): 1794-1799 (1989).

Other Reference Publication (47):

Yamashita et al., "Regulation of Human Growth Hormone Gene Expression by Insulin-like Growth Factor I in Transfected Cells", J. Biol. Chem., 262(27): 13254-13257 (1987).

Other Reference Publication (48):

Schwartz et al., "Growth hormone and insulin-like growth factors I and II produce distinct alterations in glucose metabolism in 3T3-F442A adipocytes", Proc. Natl. Acad. Sci. USA, 82: 8724-8728 (1985).

Other Reference Publication (49):

Horikawa et al., "Growth hormone and insulin-like growth factor I stimulate Leydig cell steroidogenesis", Eur. J. Pharmacol., 166: 87-94 (1989).

Other Reference Publication (50):

Rosselot et al., "Effect of Growth Hormone and Insulin-Like Growth Factor I on Cell Proliferation and Metabolic Activity of Cultured Chondrocytes", The Endocrine Society 72nd Annual Meeting, abstract 202, p. 75, of Program and Abstracts released prior to the meeting in Atlanta, GA on Jun. 20, 23, 1990.

Other Reference Publication (51):

Watanabe et al., "Characterization of a specific insulin-like growth factor-/I/somatomedin-C receptor on high density, primary monolayer cultures of bovine articular chondrocytes: regulation of receptor concentration by somatomedin insulin and growth hormone", J. Endocr., 107: 275-283 (1985).

Other Reference Publication (58):

Woodall et al., "The Effect of the Frequency of Subcutaneous Insulin-Like Growth Factor I Administration on Weight Gain in Growth Hormone Deficient Mice", Horm. Metabl. Res., 23: 581-584 (1991).